III. REMARKS

Preliminary Remarks

Reconsideration and allowance of the present application based on the following remarks are respectfully requested.

Claims 16 and 23-36 are pending in the application.

Patentability Remarks

35 U.S.C. §112, first paragraph, written description

On page 3 of the official action, the examiner rejects claims 25, 33, and 35 as allegedly failing to comply with the written description requirement of 35 U.S.C. §112, first paragraph. As described on page 3 of the application, "Other reported anti-CD20 antibodies include … anti-B1 antibody (Liu *et al.*, J. Clin. Oncol. 16:3270-8 (1998))" (*see* page 3, lines 5-8)." The Liu et al (1998) reference cited by the specification describes using the iodine-131-labeled form of anti-B1 antibody to treat relapsed B-cell lymphoma patients. The examiner alleges that since Liu et al. (1998) only describes the iodine-131-labeled form of anti-B1 antibody, the reference to "anti-B1 antibody" in the specification can only be construed to refer to the iodine-131-labeled form of anti-B1 antibody, so reference in claims 25, 33, and 35 to tositumomab (unlabeled anti-B1 antibody) allegedly lacks written descriptive support in the specification.

The applicants respectfully submit that one of skill in the art at the time of filing would clearly understand that the reference on page 3 of the specification to "anti-B1 antibody" refers to unlabeled anti-B1 antibody. At the time the application was filed, unlabeled anti-B1 antibody (tositumomab) was known to have therapeutic B cell-depleting activity (*e.g.*, *see* Shan et al., Cancer Immunol. Therapy, 2000, 48:673-83, abstract attached), and was routinely administered in combination with the iodine-131-labeled form of anti-B1 antibody in the treatment of B cell lymphoma. For example, see Koral et al., Cancer Biother. Radiopharm., 2000, 15:347-55; Vose et al., 2000, J. Clin. Oncol. 18:1316-23; and Torizuka et al., J. Nucl. Med., 2000, 41:999-1005 (abstracts attached). Moreover, in these and other scientific articles published at the time of filing, the radiolabeled form of anti-B1 antibody is clearly identified as "iodine-131-anti-B1 antibody" or "iodine-131-tositumomab." These references show that at the time of filing, persons of skill in the art commonly used the term tositumomab in published scientific articles to

refer to unlabeled anti-B1 antibody. Nothing in the published literature suggests that reference to "anti-B1 antibody" actually means iodine-131-anti-B1 antibody. Accordingly, one of skill in the art would have understood the reference to "anti-B1 antibody" on page 3 of the specification and in Liu et al. (1998) to refer to unlabeled anti-B1 antibody (tositumomab), and would have considered the applicants to be in possession of the invention of claims 25, 33 and 35 at the time the application was filed. Withdrawal of the rejection of claims 25, 33, and 35 under 35 U.S.C. §112, first paragraph, for lack of written description is therefore respectfully requested.

35 U.S.C. §112, first paragraph, enablement

On page 3 of the official action, the examiner rejects claims 29-36 under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the enablement requirement. However, on page 1 of the official action, the examiner indicates that all claims are rejected, and on page 4, lines 14-15, of the official action, the examiner states that "[t]he amended claims and the newly presented claims are now all drawn to in vivo treatment method." It is therefore unclear exactly which claims are rejected under 35 U.S.C. §112, first paragraph, for alleged lack of enablement. Notwithstanding the foregoing, the applicants submit that the specification satisfies the requirement for enablement of 35 U.S.C. §112, first paragraph, for all of the claims, and their arguments presented below in traversal of the rejection are supportive of the enablement of all of the claims.

The examiner lists the factors to be considered when determining if there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue," in accord with *In re* Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). In support of the rejection, the examiner refers to the description in Example 3 of a method for testing the anti-tumor activity of an immunoconjugate of the invention *in vivo* comprising administering from 1 μg to 10 mg of the immunoconjugate to experimental mice in which implanted solid tumors are growing, and determining dosages that inhibit tumor growth in the mice. The examiner also refers to the applicants' argument against the rejection for alleged obviousness over Davis et al. in view of Taji et al. in the previous response, in which the applicants pointed out that administration of an amount of rituximab/IFN-α-2A immunoconjugate comparable to the therapeutic dosage of rituximab described by Davis et al. (*i.e.*, four weekly infusions of 375 mg/m^2) would result in

administration of a dosage of IFN-α-2A that is more than 1600-fold greater than the dosage of soluble IFN-α-2A described by Davis et al. as being therapeutically effective. The examiner argues that since the applicants considered that a "mere 1600-fold difference" would "pose a problem" for one attempting to practice the claimed method for treating B cell lymphoma, the disclosure in Example 3 of a 10,000-fold dosage range for determining anti-tumor activity of the immunoconjugate *in vivo* would pose a similar and even greater problem to one of skill in the art attempting to practice the claimed method. *See* page 4, line 7, to page 5, line 9, of the official action. The examiner further alleges that "it is not clear what the dosages of the claimed immunoconjugate would be in order to be effective to treat B cell lymphoma," and that the specification does not provide sufficient guidance on this matter. *See* page 5, lines 9-11, of the official action. The examiner concludes that in consideration of the unpredictable state of the art, the limited guidance and lack of examples in the specification showing how to use the claimed invention, and the broad breadth of the claims, undue experimentation would have been required in order for one of skill in the art to successfully perform the claimed method . *See* page 5, lines 12-14, of the official action.

The applicants respectfully submit that the specification describes the claimed method with sufficient detail that one of skill in the art would <u>not</u> have had to perform undue experimentation in order to practice the claimed method successfully.

> The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation. *See* In re Wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988); *also* United States v. Telectronics, Inc., 857 F.2d 778, 785, 8 USPQ2d 1217, 1223 (Fed. Cir. 1988).
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> As long as the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement of 35 U.S.C. 112 is satisfied. In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).
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> A patent need not teach, and preferably omits, what is well known in the art. *See* In re Buchner, 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991); also Hybritech, Inc. v. Monoclonal Antibodies , Inc ., 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986), cert. denied, 480 U.S. 947 (1987).

> The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. *See* In re Certain Limited-Charge Cell Culture Microcarriers, 221 USPQ 1165, 1174 (Int'l Trade Comm'n 1983), aff'd. sub nom., Massachusetts Institute of Technology v. A.B. Fortia, 774 F.2d 1104, 227 USPQ 428 (Fed. Cir. 1985); *also* In re Wands, 858 F.2d at 737, 8 USPQ2d at 1404. The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. In re Angstadt, 537 F.2d 498, 504, 190 USPQ 214, 219 (CCPA 1976).
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> If a statement of utility in the specification contains within it a connotation of how to use, and/or the art recognizes that standard modes of administration are known and contemplated, 35 U.S.C. 112 is satisfied. In re Johnson, 282 F.2d 370, 373, 127 USPQ 216, 219 (CCPA 1960); In re Hitchings, 342 F.2d 80, 87, 144 USPQ 637, 643 (CCPA 1965). See also In re Brana, 51 F.2d 1560, 1566, 34 USPQ2d 1437, 1441 (Fed. Cir. 1993).
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> Determining enablement is a question of law based on underlying factual findings. In re Vaeck, 947 F.2d 488, 495, 20 USPQ2d 1438, 1444 (Fed. Cir. 1991); Atlas Powder Co. v. E.I. du Pont de Nemours & Co., 750 F.2d 1569, 1576, 224 USPQ 409, 413 (Fed. Cir. 1984).
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> *See* M.P.E.P. § 2164.01

The applicants respectfully submit that the eight factors set forth in *In re* Wands (858 F.2d 731, 737, 8 USPQ2d 1400, 1404, Fed. Cir. 1988) support the conclusion that the specification satisfies the enablement requirement of 35 U.S.C. §112, first paragraph, and that any necessary experimentation that is required to practice the claimed invention successfully is not "undue."

With regard to the first factor, the breadth of the claims, it is noted that independent claims 16 and 29 are both directed to a method comprising administering a therapeutically effective amount of an immunoconjugate to the subject, wherein the immunoconjugate comprises an anti-CD20 antibody or an immunogenic fragment thereof that binds to CD20 expressed by a B cell lymphoma cell in the subject, and wherein said anti-CD20 antibody or immunogenic fragment thereof possesses human effector function, and is fused at its carboxy terminus to interferon-α-2a (IFN-α-2a) that binds a receptor expressed on the surface of an effector cell. At the time the application was filed, it was well-known that anti-CD20 antibodies can be used to kill B cell lymphoma cells and to treat B cell lymphoma. Several known anti-

CD20 antibodies are described on page 3, lines 1-12. As indicated in the paragraph at the bottom of page 9, the structures of antibodies, the specific antibody sites that bind to Fc receptors and complement proteins (e.g., $C1_q$), and the roles of antibodies in mediating effector functions as described were well known at the time of filing. The structure of IFN-α-2a and its role in stimulating cell-killing effector activity by effector cells such as natural killer cells and macrophages was also well known at the time of filing. Accordingly, one of skill in the art would have known how to prepare the immunoconjugate of the claimed invention comprising an anti-CD20 antibody or an immunogenic fragment thereof that binds to CD20 and possesses human effector function, and is fused at its carboxy terminus to interferon-α-2a (IFN-α-2a) that binds a receptor expressed on the surface of an effector cell, without undue experimentation.

Claim 16 is directed to a method of killing a B cell lymphoma cell in a subject, and claim 29 is directed to a method of treating B cell lymphoma in a subject, comprising administering a therapeutically effective amount of the immunoconjugate to the subject. Although the application does not disclose the dosage of the anti-CD20 antibody/IFN-α-2a immunoconjugate that is administered in order to kill B cell lymphoma cells and treat B cell lymphoma in a subject, methods for determining safe and effective dosage of a therapeutic anti-CD20 antibody for the treatment of B cell lymphoma were known at the time the application was filed. One of skill in the art would therefore have been able to determine a therapeutically effective and safe dosage of the anti-CD20 antibody/IFN-α-2a immunoconjugate in order to practice the claimed invention without having to perform undue experimentation.

The second factor to be considered is the nature of the invention. The claimed invention is a method for killing B cell lymphoma cells and treating B cell lymphoma in a subject comprising administering a therapeutically effective amount of an immunoconjugate to the subject, wherein the immunoconjugate comprises an anti-CD20 antibody or an immunogenic fragment thereof that binds to CD20 expressed by a B cell lymphoma cell in the subject, and wherein said anti-CD20 antibody or immunogenic fragment thereof possesses human effector function, and is fused at its carboxy terminus to interferon-α-2a (IFN-α-2a) that binds a receptor expressed on the surface of an effector cell. As discussed above, one of skill in the art at the time of filing would have known how to make an anti-CD20 antibody/IFN-α-2a immunoconjugate of the claimed invention, and would also have been able to use known methods for determining a therapeutically effective dosage of a B cell-depleting antibody for treatment of B cell lymphoma

to determine a therapeutically effective dosage of the anti-CD20 antibody/IFN-α-2a immunoconjugate in order to practice the claimed invention, without having to perform undue experimentation.

With regard to the third factor, the state of the prior art, methods for preparing fusion proteins comprising an antibody conjugated to a cytokine were known at the time of filing, as described on pages 6-7 of the specification. As discussed above, methods for determining a safe and effective dosage of a therapeutic anti-CD20 antibody for the treatment of B cell lymphoma that could be used to determine a therapeutically effective and safe dosage of an anti-CD20 antibody/IFN-α-2a immunoconjugate in order to practice the claimed invention were also known at the time the application was filed.

As discussed in the previous response, Davis et al. described a method for treating B cell lymphoma comprising separately administering doses of soluble rituximab and of soluble IFN-α-2A. In the previous response, the applicants noted that administration of an amount of rituximab/IFN-α-2A immunoconjugate comparable to the therapeutic dosage of rituximab described by Davis et al. would result in administration of a dosage of IFN-α-2A that is more than 1600-fold greater than the dosage of soluble IFN-α-2A described by Davis et al. as being therapeutically effective. The applicants argued that it would not have been obvious to modify the method of Davis et al. by making and administering a rituximab/IFN-α-2A immunoconjugate according to the claimed invention, because one of ordinary skill in the art could not predict if the rituximab and IFN-α-2a proteins present in a fusion protein would show pharmacological activities comparable to those of the soluble proteins, and would have considered the two methods to be qualitatively different in view of the 1600-fold difference in dosage of IFN-α-2a provided by the method of Davis et al. relative to the modified method comprising administering the immunoconjugate. The examiner has compared the 1600-fold difference in IFN-α-2a dosage discussed in the previous response to the 10,000-fold dosage range for determining anti-tumor activity of the immunoconjugate *in vivo* described in Example 3, as if both numbers refer to the range of dosages one of skill in the art would test in determining a therapeutically effective (and safe) dosage of the anti-CD20 antibody/IFN-α-2a immunoconjugate in order to practice the claimed invention. As discussed above, this is a mischaracterization of the argument for non-obviousness presented in the previous response. It is also a mischaracterization of the teachings of Example 3, and of the known procedures that one of skill in the art would follow in

determining a therapeutically effective dosage of the anti-CD20 antibody/IFN-α-2a immunoconjugate to be administered in practicing the claimed invention. As noted above, Example 3 discloses a method for testing the anti-tumor activity of an immunoconjugate of the invention *in vivo* comprising intravenously injecting from 1 μg to 10 mg of the immunoconjugate into experimental mice in which implanted solid tumors are growing, and determining dosages that inhibit the growth of the tumors in the mice. One of skill in the art would understand that multiple factors determine the dosages that inhibit tumor growth, including the structure of the immunoconjugate and the genotype and phenotype of the tumor cells, and that it is common practice to test a wide range of dosages of an agent of undetermined anti-tumor activity in experimental animals, in order to obtain as much data as possible. For example, it is well known that a compound that only shows anti-tumor activity against one type of tumor in mice when administered at high dosage may be found to have high anti-tumor activity at low dosage when used to against a different type of tumor. One of skill in the art would also know that the safety of the patient is a primary concern in performing phase I, II, and III clinical trials to determine a therapeutically effective and safe dosage of the anti-CD20 antibody/IFN-α-2a immunoconjugate to be administered in practicing the claimed invention in human subjects. One of skill in the art would therefore understand that the 10,000-fold dosage range described in Experiment 3 for treating experimental mice would not be used in clinical trials in which effective dosage for human patients is determined.

The fourth factor to be considered is the level of one of ordinary skill. One of skill in the art of making and using antibodies and immunoconjugates for treating cancer typically has a very high level of skill and experience, and has a M.D. degree and/or a Ph.D. degree in a medical field.

The fifth factor is the level of predictability in the art. Persons of skill in the art recognize that there is a relatively high level of unpredictability in the field of treating cancer. Each individual patient and each tumor responds to a given treatment in a unique and generally unpredictable manner, so persons of skill in the art describe success and failure of cancer treatment in statistical terms.

The sixth factor to be considered is the amount of direction provided by the inventors. The specification provides a detailed description of the structure and functionality of the anti-CD20 antibody/IFN-α-2a immunoconjugate of the claimed invention, so that one of skill in the

art would be able to make it without undue experimentation. In particular, the application teaches that the antibody of the invention is an anti-CD20 antibody that possesses human effector function; *i.e.*, it retains those portions of the constant domain that bind Fc receptor and/or complement. The specification further describes the immunoconjugate of the invention as one in which the IFN-α-2a molecule is attached to the carboxy terminus of the antibody, with the IFN-α-2a molecule retaining the ability to bind to its receptor and activate an effector cell. For example, *see* page 9, lines 20-29. In addition to the *in vivo* assay described in Example 3, the specification describes an *in vitro* assay for identifying immunoconjugates according to the disclosed invention that have anti-tumor activity and are "therapeutically effective," comprising screening to identify immunoconjugates that inhibit *in vitro* growth of target tumor cells by greater than about 20%, at a concentration of about 0.1 to 3.0 μg/ml of the immunoconjugate (a 30-fold range). *See* the paragraph bridging pages 13-14.

With regard to the seventh factor, the existence of working examples, the application does not provide a working example of the claimed invention. However, an applicant need not have actually reduced the invention to practice prior to filing (*see* Gould v. Quigg, 822 F.2d 1074, 1078, 3 USPQ 2d 1302, 1304 (Fed. Cir. 1987)) and the specification need not contain an example if the invention is otherwise disclosed in such manner that one skilled in the art will be able to practice it without an undue amount of experimentation. In re Borkowski, 422 F.2d 904, 908, 164 USPQ 642, 645 (CCPA 1970). *See* M.P.E.P. § 2164.02.

The eighth factor to be considered is the quantity of experimentation needed to make or use the invention based on the content of the disclosure. As discussed above with above respect to first, second, third, and sixth factors, one of skill in the art would have known how to use known methods to successfully prepare an anti-CD20 antibody/IFN-α-2a immunoconjugate of the claimed invention without undue experimentation. One of skill in the art would also have known how to use established and reliable methods for determining a therapeutically effective dosage of the anti-CD20 antibody/IFN-α-2a immunoconjugate to be administered in successfully practicing the claimed invention. Accordingly, one of skill in the art would not have had to perform undue experimentation in order to successfully practice the claimed method. Withdrawal of the rejection of claims 29-36 under 35 U.S.C. §112, first paragraph, for alleged lack of enablement is therefore respectfully requested.

Double patenting

On page 5 of the official action, the examiner objects to claim 35 under 37 C.F.R. §1.75 as being a duplicate of claim 33.

The applicants respectfully submit that claims 33 and 35 are directed to patentably distinct embodiments of the claimed invention. Claim 33 is directed to the method of claim 29, wherein the anti-CD20 antibody is ibritumomab, which is an antibody that is identified in the application as the murine counterpart to rituximab (*see* page 3, lines 3-4). On the other hand, claim 35 is directed to the method of claim 29, wherein the anti-CD20 antibody is tositumomab, which term refers to anti-B1 antibody, as discussed above. As claims 33 and 35 specify separate and distinct anti-CD20 antibodies, withdrawal of the objection to claim 35 under 37 C.F.R. §1.75 as being duplicative of claim 33 is respectfully requested.

IV. CONCLUSION

All rejections having been addressed, it is respectfully submitted that the present application is in condition for allowance and a Notice to that effect is earnestly solicited. If the examiner identifies any points that he feels may be best resolved through a personal or telephone interview, he is kindly requested to contact the undersigned attorney at the telephone number listed below.

Please charge any fees or credit any overpayments associated with the submission of this response to Deposit Account Number 03-3975.

Respectfully submitted,

/ thomas a cawley jr /

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